Cervical Cancer

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Epidemiology

- The most common gynecologic malignancy in the world
- The second most frequently diagnosed cancer in women worldwide after breast cancer.
- Majority of cases occur in developing countries.
- In USA cervical cancer is the third most common gynecologic malignancy and the third most common cause of gynecologic cancer death.

Epidemiology

- Mortality and incidence rates for cervical cancer have declined in most developed countries.
- Mostly attributed to the introduction of routine Papanicolaou smear (pap test) screening.
- 60% of women who develop cervical cancer in developed countries have either never been screened or have not been screened in the preceding 5 years.
- The mean age for cervical cancer is 52.2 years, and the distribution of cases is bimodal, with peaks at 35 to 39 years and 60 to 64 years.

Risk Factors

- Race and Socioeconomic Status.
  - The incidence rate is higher in Blacks than that among white women,
  - Partially accounted for by the strong inverse association between cervical cancer incidence and socioeconomic factors.
  - Racial differences are also apparent in survival;

- Risk factors for cervical cancer are essentially related to exposure to human papilloma virus (HPV), smoking, and immuno-suppression.

Risk Factors

- HPV. HPV infection is present in 99.7% of all cervical cancers.
- Cigarette smoking is an independent risk factor in the development of cervical disease. 4.5-fold increased risk of carcinoma in situ (CIS) compared with matched controls.
- Increased risk of cervical cancer has been noted in women exposed passively to tobacco smoke.
- Immunocompromised women may be at higher risk of developing cervical cancer and may demonstrate more rapid progression from preinvasive to invasive lesions.

Clinical Presentation

- The most common presenting symptom of invasive cervical cancer is abnormal vaginal bleeding and discharge.
- Abnormal vaginal bleeding may take the form of postcoital bleeding, intermenstrual, or postmenopausal bleeding.
- It could be asymptomatic, especially in sexually inactive women, when the disease is quite advanced.
- Serosanguineous or yellowish vaginal discharge, at times foul smelling, may occur particularly in large tumors.
- Premenopausal patients may develop hematometra due to occlusion of the endocervical canal by a cancer.

Clinical Presentation

- Other patients may present with symptomatic anemia or pelvic pain.
- Sciatic and back pain can be related to sidewall extension, hydronephrosis, or metastasis.
- Bladder or rectal invasion by advanced-stage disease may produce urinary or rectal symptoms (e.g., vaginal passage of stool or urine, hematuria, urinary frequency, hematochezia).
- Advanced disease may also cause lower extremity swelling from occlusion of pelvic lymphatics or thrombosis of the external iliac vein.

Clinical Presentation, Signs.

- Early invasive disease may not be detected clinically
- Most women with cervical cancer have a visible cervical lesion.
- On speculum examination, cervical cancer may appear as an exophytic cervical mass that characteristically bleeds on contact.
- Endophytic tumors develop entirely within the endocervical canal, and the external cervix may appear normal.

Clinical Presentation, Signs.

- Bimanual examination may reveal a firm, indurated, an often barrel-shaped cervix.
- The vagina should be inspected for extension of disease.
- Rectal exam provides information regarding the nodularity of the uterosacra ligaments and helps determine extension of disease into the parametrium.

Diagnosis

- Obvious exophytic lesions, cervical biopsy is usually all that is needed for histologic confirmation.

- In patients with a grossly normal appearing cervix and with abnormal cytology on pap smear, colposcopic examination with directed biopsies and endocervical curettage (ECC) is necessary .

- If a definite diagnosis of cervical cancer cannot be made on the basis of office biopsies, diagnostic cervical conization may be necessary.

Spread of Disease

- **Direct Extension.** into the parametria, vagina, uterine corpus, peritoneal cavity, bladder, or rectum.
  - Parametrial Extension.
  - Vaginal Extension.
  - Bladder and Rectal Involvement.

- **Lymphatic Spread.** First station nodes are: obturator, external iliac, hypogastric, parametrial, presacral, and common iliac. Para-aortic nodes are second station.

- **Blood-Borne Metastasis.**

Cervical Cancer staging

Table 1
Carcinoma of the cervix uteri: FIGO nomenclature (Montreal, 1994)

Stage 0	Carcinoma *in situ*, cervical intraepithelial neoplasia Grade III.
Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded).
Ia	Invasive carcinoma which can be diagnosed only by microscopy. All macroscopically visible lesions – even with superficial invasion – are allotted to Stage Ib carcinomas. Invasion is limited to a measured stromal invasion with a maximal depth of 5.0 mm and a horizontal extension of not >7.0 mm. Depth of invasion should not be >5.0 mm taken from the base of the epithelium of the original tissue – superficial or glandular. The involvement of vascular spaces – venous or lymphatic – should not change the stage allotment.
Ia1	Measured stromal invasion of not >3.0 mm in depth and extension of not >7.0 mm.
Ia2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm.
Ib	Clinically visible lesions limited to the cervix uteri or preclinical cancers greater than Stage Ia.
Ib1	Clinically visible lesions not >4.0 cm.
Ib2	Clinically visible lesions >4.0 cm.

Cervical Cancer staging

Stage II	Cervical carcinoma invades beyond uterus, but not to the pelvic wall or to the lower third of vagina.
	IIa No obvious parametrial involvement.
	IIb Obvious parametrial involvement.
Stage III	The carcinoma has extended to the pelvic wall. On rectal examination, there is no cancer-free space between the tumor and the pelvic wall. The tumor involves the lower third of the vagina. All cases with hydronephrosis or nonfunctioning kidney are included, unless they are known to be due to other cause.
	IIIa Tumor involves lower third of the vagina, with no extension to the pelvic wall.
	IIIb Extension to the pelvic wall and/or hydronephrosis or nonfunctioning kidney.
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV.
	IVa Spread of the growth to adjacent organs.
	IVb Spread to distant organs.

Cervical Cancer Staging 2008

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion ≤5 mm and largest extension ≥ 7 mm
IA1	Measured stromal invasion of ≤3.0 mm in depth and extension of ≤ 7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not >7.0 mm
IB	Clinically visible lesions limited to the cervix uteri or pre-clinical cancers greater than stage IA *
IB1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IB2	Clinically visible lesion >4.0 cm in greatest dimension
Stage II	Cervical carcinoma invades beyond the uterus, but not to the pelvic wall or to the lower third of the vagina
IIA	Without parametrial invasion
IIA1	Clinically visible lesion ≤ 4.0 cm in greatest dimension
IIA2	Clinically visible lesion >4 cm in greatest dimension
IIB	With obvious parametrial invasion
Stage III	The tumor extends to the pelvic wall and/or involves lower third of the vagina and/or causes hydronephrosis or non-functioning kidney **
IIIA	Tumor involves lower third of the vagina, with no extension to the pelvic wall
IIIB	Extension to the pelvic wall and/or hydronephrosis or non-functioning kidney
Stage IV	The carcinoma has extended beyond the true pelvis or has involved (biopsy proven) the mucosa of the bladder or rectum. A bullous edema, as such, does not permit a case to be allotted to Stage IV
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

Cervical Cancer Staging 2008

Stage I	The carcinoma is strictly confined to the cervix (extension to the corpus would be disregarded)
IA	Invasive carcinoma which can be diagnosed only by microscopy, with deepest invasion <5 mm and largest extension ≥ 7 mm
IA1	Measured stromal invasion of <3.0 mm in depth and extension of ≤ 7.0 mm
IA2	Measured stromal invasion of >3.0 mm and not >5.0 mm with an extension of not > 7.0 mm

Cervical Cancer Staging 2008

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Cervical Cancer Staging 2008

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IIB	With obvious parametrial invasion

Cervical Cancer Staging 2008

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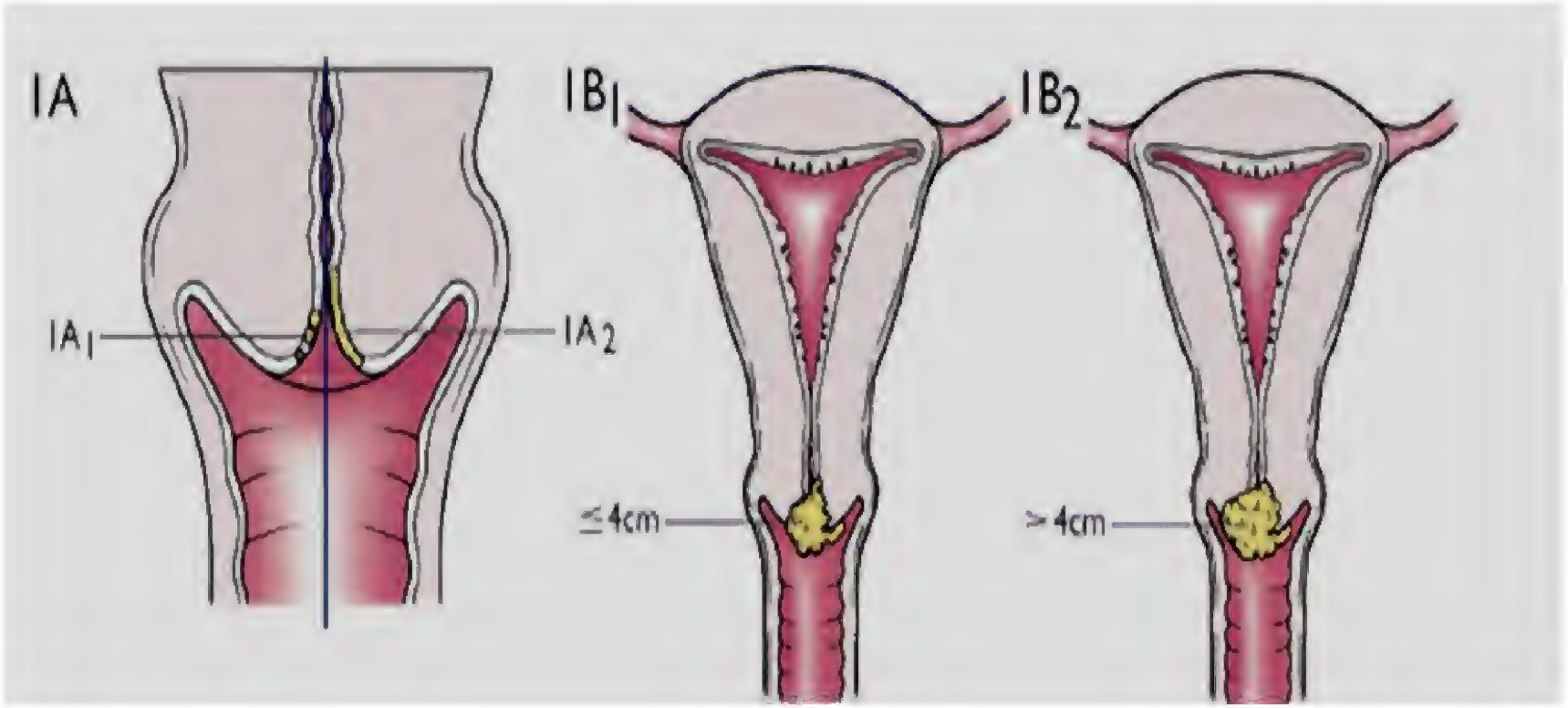
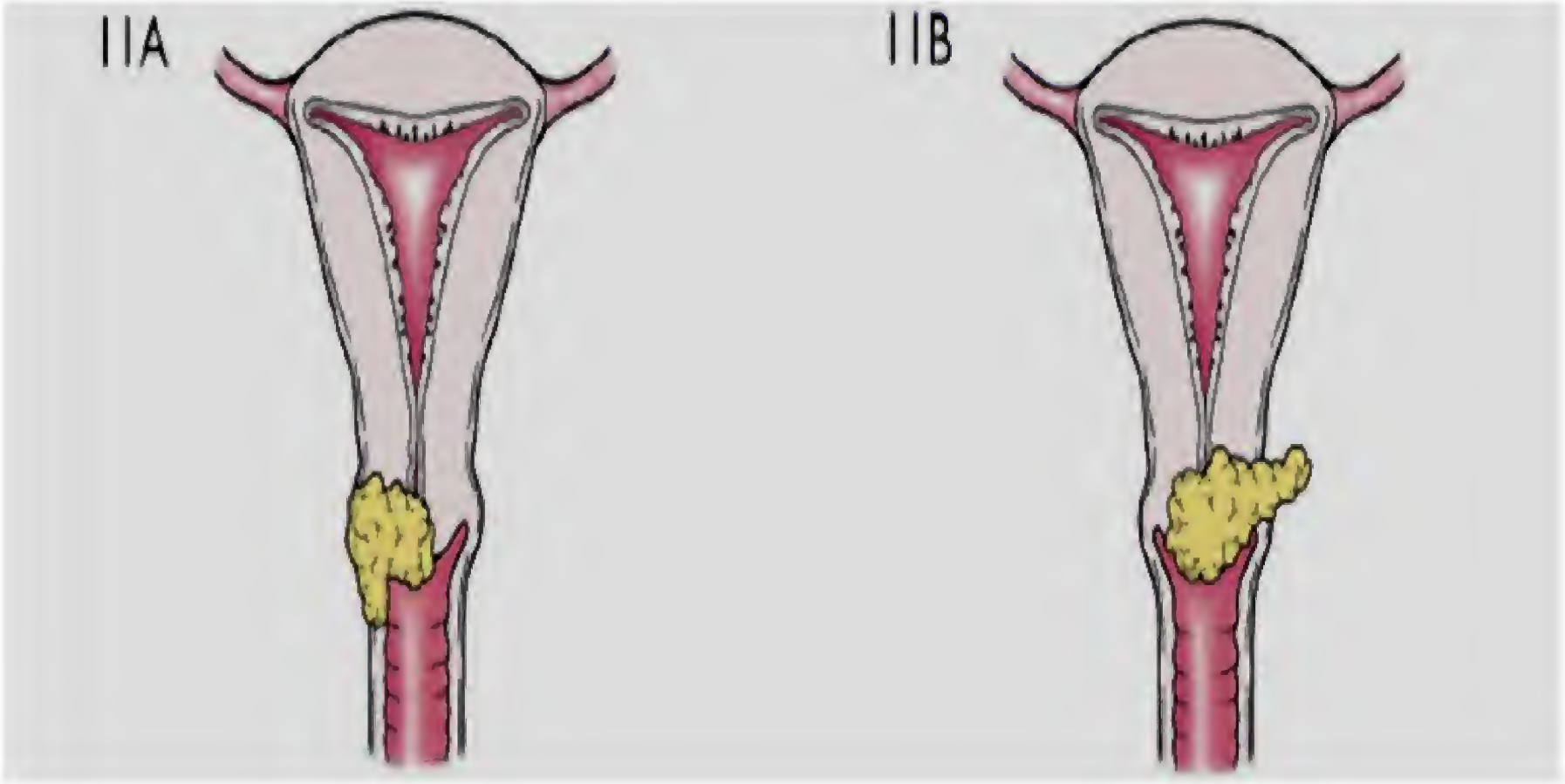
IVA	Spread of the growth to adjacent organs
IVB	Spread to distant organs

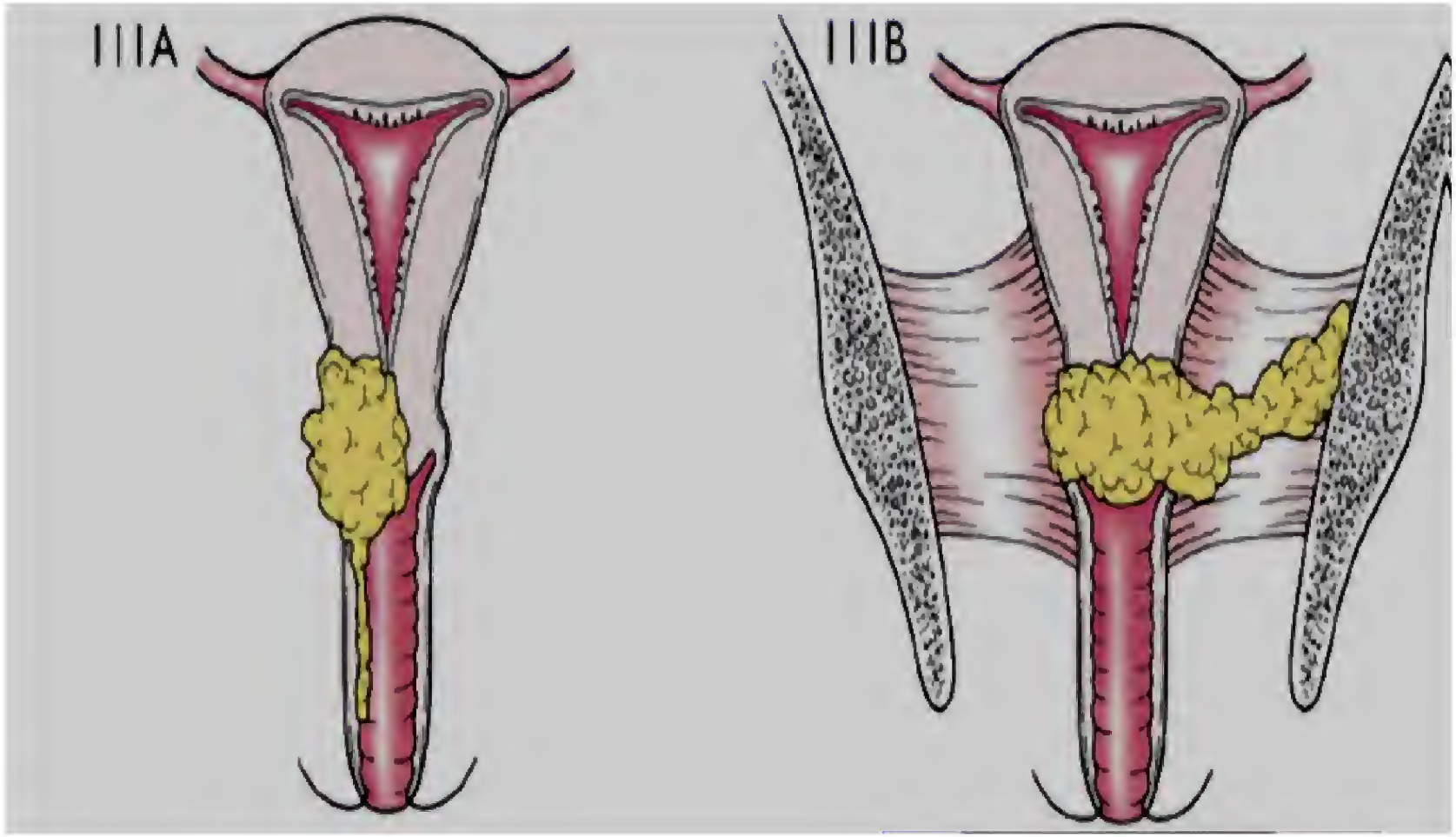
Stage I



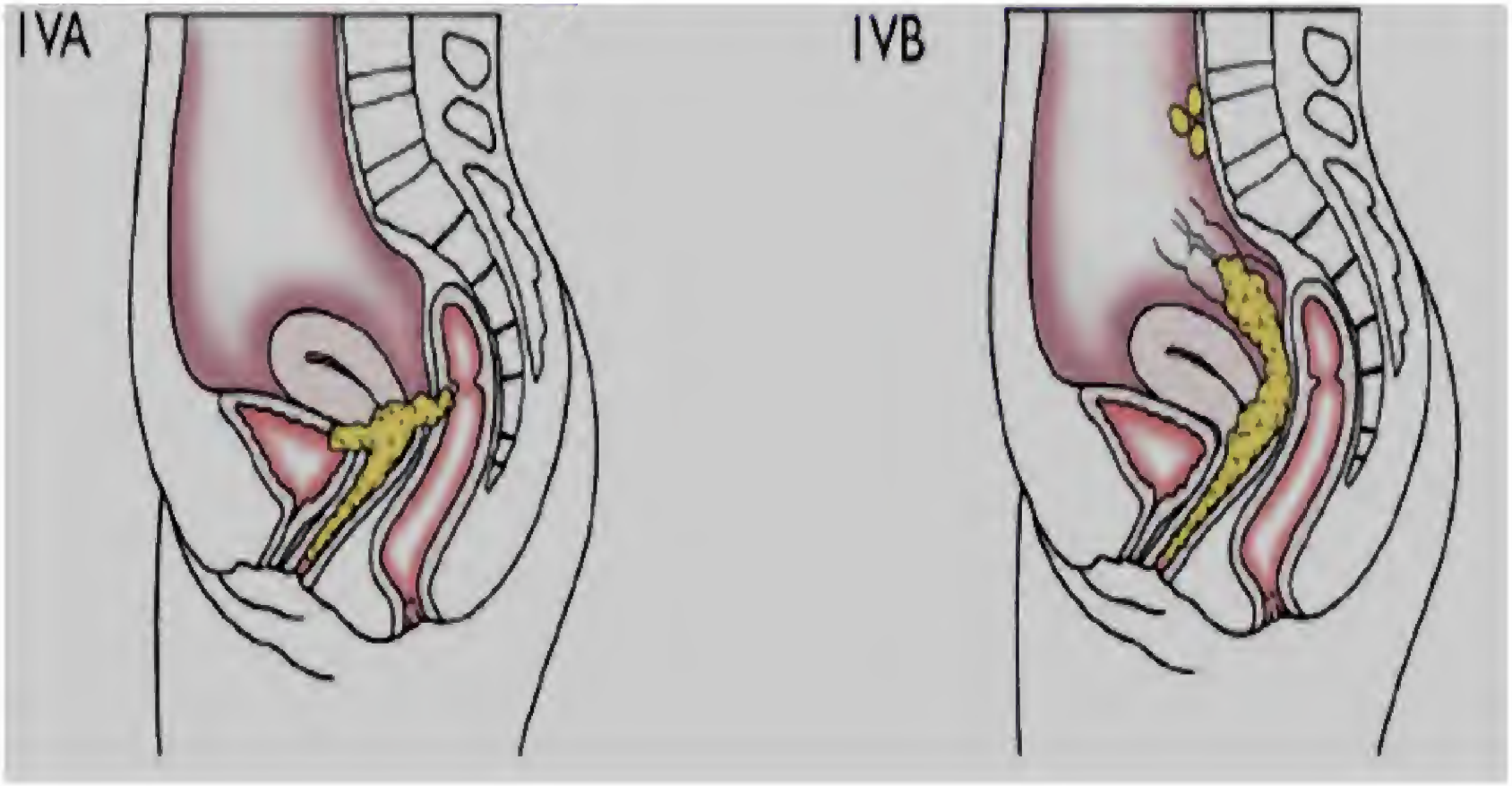
Stage II



Stage III



Stage IV



Staging

- Clinico-pathological
- Surgical (Laparoscopic)
- Radiological (MRI)

- The distribution of patients by clinical stage is as follows:
  - 38% stage I,
  - 32% stage II,
  - 25% stage III
  - 4% stage IV

Histologic subtypes

- Squamous cell carcinomas 80-90%
  - large cell keratinizing,
  - large cell non-keratinizing
  - Small cell squamous
  - verrucous carcinoma
- Adenocarcinomas (5-10%)
- Adenosuamous
- Small cell carcinomas
- Rare Types

Prognostic factors

- Stage
- Histological type
- Tumour grade
- Nodal status
- Tumour volume
- Depth of invasion
- Lymph-vascular space involvement

Treatment

- Specialist referral (gynecological oncology specialist)

- Multidisciplinary management

Treatment

- **Surgical: (conventional vs. laparoscopic)**
  - Conization
  - Radical Trachelectomy
  - Radical hysterectomy
  - Exentration
- **Radiotherapy:**
  - Primary or adjuvant
  - Whole pelvis external
  - Brachytherapy
- **Chemotherapy:**
  - Neoadjuvant chemotherapy
  - Combined radio-chemotherapy
- **Multiodal**
- **Palliative treatment**

Surgical Treatment

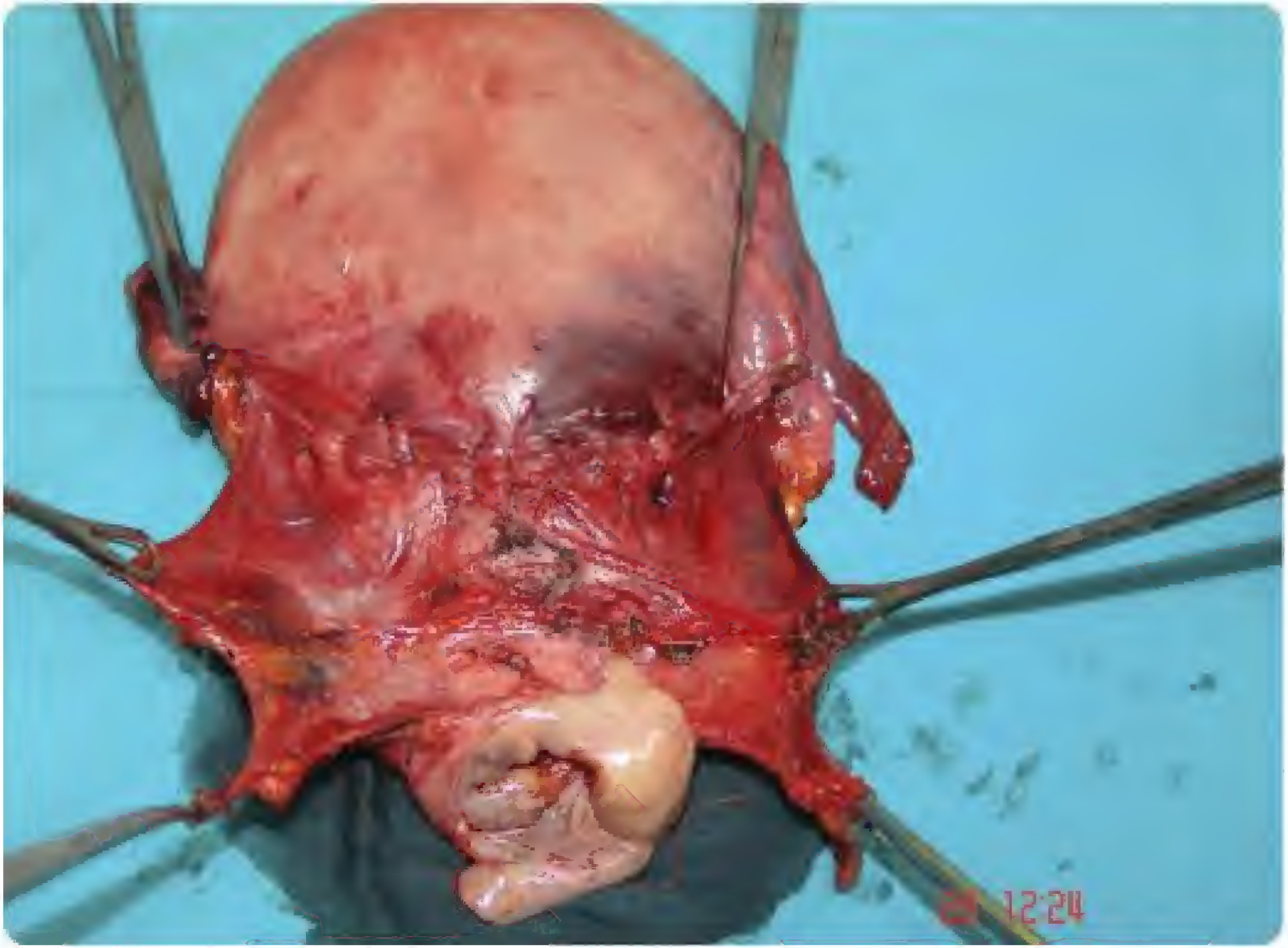
- Radical surgery is recommended for FIGO IB1 disease if there are no contraindications to surgery.
- Removal of pelvic lymph nodes is not recommended during treatment for FIGO IA1 disease.
- Pelvic lymph nodes should be removed if FIGO IA2 disease is present.
- Women requesting fertility conservation should be offered radical trachelectomy and pelvic lymph node dissection, providing the tumour diameter is less than 2 cm and no lymphatic-vascular space invasion is present.

Surgical Treatment

Women with early stage disease and no LVSI (FIGO IA2 and microscopic IB1) requesting fertility conservation maybe offered cold knife conisation or large loop excision of the transformation zone combined with pelvic lymph node dissection.

Laparoscopic-vaginal radical hysterectomy should not be offered to patients with tumour diameter greater than 2 cm

Surgical treatment.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Complications

- Complications of disease
  - Haemorrhage
  - Lymphoedema
  - Fistulae
  - Ureteric obstruction
  - Renal failure
- Complications of treatment

chemoradiotherapy/radiotherapy

- Any patient with cervical cancer considered suitable for radical radiotherapy treatment should have concurrent chemoradiotherapy with a platinum based chemotherapy, if fit enough.
- Patients who have undergone surgery for cervical carcinoma and have positive nodes should be considered for adjuvant treatment with concurrent chemoradiotherapy with platinum based chemotherapy.
- Concurrent chemoradiation should be considered in preference to radiation alone.
- Brachytherapy should be considered an essential component of radical radiotherapy or chemoradiotherapy

chemoradiotherapy/radiotherapy

- Patients who have undergone surgery for cervical carcinoma, have negative nodes and any two of the following risk factors should be considered for adjuvant treatment with radiotherapy, if fit enough:
  - greater than a third stromal invasion
  - lymphovascular space invasion
  - tumour diameter of >4 cm.

chemoradiotherapy/radiotherapy

- Treatment of anaemia
- Treatment of radiation induced complications
- Hormone replacement therapy
- Sexual morbidity management

Follow up after treatment

- Patients should be followed up every four months for at least two years.
- History taking and clinical examination should be carried out during follow up of patients with cervical cancer to detect symptomatic and asymptomatic recurrence.
- Cervical cytology or vault smears are not indicated to detect asymptomatic recurrence of cervical cancer.
- Imaging (CT, MRI) is indicated for to assess suspected recurrent disease.

Management of recurrent disease

- Pelvic exenteration should be reserved as salvage surgery for women with recurrent cervical cancer in the central pelvis whose chemoradiotherapy has failed.

- Palliative chemotherapy should be offered to women with FIGO stage IVB or recurrent cervical carcinoma, after discussion of the relative benefits and risks

Treatment during pregnancy

- For pregnant women with cervical cancer, the choice of therapeutic modality should be decided in the same manner as for non-pregnant patients.
- For pregnant women diagnosed with cervical cancer before 16 weeks of gestation, immediate treatment is recommended.
- For pregnant women with early stage disease (FIGO IA1, IA2, IB) diagnosed after 16 weeks of gestation, treatment may be delayed to allow fetal maturity to occur.

Treatment during pregnancy

For pregnant women with advanced disease (FIGO 1B2 or greater) diagnosed after 16 weeks of gestation, consideration for delay must be based on gestational age at time of diagnosis.

An individualised treatment plan should be determined, in consultation with the patient, by the multidisciplinary team, which should include an obstetrician.